REMARKS

Claims 3-11, 15-20, 24-34, 38, 40-48, 52-57 and 61-71 have been amended to clarify the claimed subject matter. No new matter is added by the amendments to the claims. Claims 1-74 remain pending.

Scope of Examination

The Examiner has indicated that claims 38-74 were examined only for SEQ ID NO:200. Applicants have amended claims 38-74 to recite the HRGDF73 cDNA of ATCC Deposit No. 97904.

Information Disclosure Statement

The Examiner has indicated that references AB-AE and AM-AN were not considered as filed with the Information Disclosure Statement submitted on October 19, 2001 because the entire documents were not obtained by the Examiner. Applicants submit herewith a Supplemental Information Disclosure Statement and complete copies of references AB-AE and AM-AN.

Rejections under 35 U.S.C. §112, second paragraph

Claims 3-7, 10-11, 19-20, 26-30, 33-34 and 38-74 were rejected under 35 U.S.C. §112, second paragraph as indefinite. Although Applicants respectfully disagree, in the interest of furthering prosecution on the merits, the claims have been amended as follows: with respect to the rejections relating to the "portion thereof" and "labeled antibody" terminology, Applicants have amended the claims as suggested by the Examiner; with respect to ATCC Deposit No. 97904, Applicants have amended the claims to specify the HRGDF73 cDNA of ATCC Deposit No. 97904. Applicants respectfully submit that the amendments to the claims overcome this rejection.

Rejections under 35 U.S.C. §101/§112, first paragraph

Claims 1-74 were rejected under 35 U.S.C. §101 as lacking a specific and/or substantial or well established utility. A corresponding rejection under 35 U.S.C. §112, first paragraph was also issued. Applicants respectfully traverse.

To aid in the following discussion of utility, Applicants will first provide a brief overview of B-cell development. Briefly, B-lymphocytes mature from hematopoietic stem cells through a series of developmental stages. An early checkpoint is the transition from the pro-B to the pre-B cell stage. In precursor B (pre-B) lymphocytes, surface expression of a pre-B cell receptor (pre-BCR) is necessary for cell proliferation, repertoire selection, and allelic exclusion. *See*, Rosnet et al., J. Biol. Chem., 279(11)10228-10236 (2004) at page 10288, column 1. *See also,* Hess et al., PNAS, 98(4):1745-1750 (2001) at page 1745, column 1 (B-cell differentiation and proliferation is blocked at the pro-B cell stage in mutant mice that are unable to assemble a "functional" pre-B cell receptor (pre-BCR)). A "functional" pre-BCR consists of an antigen-binding subunit made of two covalently associated μ or δ immunoglobulin (Ig) heavy chains (HC), each covalently bound to an Ig light chain (LC). This dimer is bound to an Igα/Igβ signal transduction heterodimer, which makes up the signaling unit of the BCR. In pre-B cells, a surrogate light chain, which includes a ***VpreB*** and λ5 proteins substitutes for the conventional light chain [emphasis added]. *See*, Rosnet et al., J. Biol. Chem., 279(11)10228-10236 (2004) at page 10288, column 2.

The application discloses a human homolog of the mouse VpreB3 (8HS20) protein. According to the disclosure, the VpreB3 protein is expressed as a surface receptor primarily in human B-cells, and to a lesser extent in Hodgkin's lymphoma. Subsequent publications confirm that the disclosed VpreB3 protein is an essential component of the pre-BCR and is expressed at high levels from the pro-B to the immature B-cell stage. *See,* Rosnet et al., J. Biol. Chem., 279(11)10228-10236 (2004), at page 10288, column 2, second paragraph. Thus, the claimed antibodies can be used to target B-cells from the pro-B to the immature B-cell stage, for treatment and/or diagnosis of B-cell disorders, such as Hodgkin's Lymphoma, Common Variable Immunodeficiency, and/or other B-cell

lymphomas, as disclosed in the specification at page 98, first paragraph. Applicants therefore submit that the application includes a specific, substantial and credible assertion of utility.

The test for determining whether an asserted utility is specific is whether the asserted utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention, such as use of a complex machine for landfill. *See*, Utility Examination Guidelines. The application discloses that polynucleotides and/or polypeptides, and hence, antibodies thereto, are useful as reagents for treatment and diagnosis of diseases and conditions that include, Hodgkin's Lymphoma, Common Variable Immunodeficiency, and/or other B-cell lymphomas. These utilities are specific, in that not every protein may be used to treat and/or diagnose the listed diseases.

Moreover, the disclosed utilities are substantial. "[T]he general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See*, Revised Interim Utility Guidelines Training Materials, page 6. As discussed above, the application discloses use of polynucleotides and/or polypeptides, and antibodies thereto, as reagents for treatment or diagnosis of specific diseases such as Hodgkin's Lymphoma, Common Variable Immunodeficiency, and/or other B-cell lymphomas. Accordingly, the utilities asserted by Applicants are clearly substantial.

In assessing the credibility of the asserted utilities, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, "question") the truth of the statement of utility. *See,* M.P.E.P. § 2107 at 2100-30 and 2100-40; *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995); and, *In re* Cortright, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). Thus, the Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *See id.* Such a *prima facie* showing must contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not specific, substantial, and credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.*

In the utility rejection asserted by the Examiner, the Examiner notes that Rosnet et al., Cytogenet. Cell Genet., 87:205-208 (1999) indicate that the precise function of VpreB3 is not known (page 205, column 2, lines 7-9) and concludes that the claimed invention has no utility. Applicants respectfully submit that the function of VpreB3 is not critical to the instant determination of utility.

Other successful anti-cancer drugs have been developed against cell surface antigens for which the function is or was unknown. For example, Rituximab (manufactured by Genentech under the name Rituxan®) is a monoclonal antibody that binds specifically the CD20 surface antigen found on both healthy and diseased B-cells. Rituximab is used for the treatment of patients with B-cell non-Hodgkin's lymphoma. *See,* O'Neal, Clin. J. Oncol. Nursing, 5(2):75-76 (2001). Rituximab was developed as an effective treatment for inducing cell death and sensitizing cells to chemotherapy, *even though the function of CD-20 was not known. See, e.g.,* Riley et al., Semin Oncol. (27)6-12:17-24 (2000), abstract.

Similar to CD20, it is known that the VpreB3 protein is expressed on the surface of B-cells. Thus, antibodies that recognize VpreB3 are useful for targeting cytotoxic agents to B-cells, for example, for the treatment and/or diagnosis of B-cell disorders such as Hodgkin's Lymphoma, Common Variable Immunodeficiency, and other B-cell lymphomas.

It is applicant's position that Rosnet et al., in fact, supports Applicants asserted utility by confirming that other skilled artisans would not "doubt" or "question" that the gene is a human ortholog of mouse VpreB3. Applicants therefore respectfully submit that the Examiner has not met the burden necessary establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

In the rejection under 35 U.S.C. §101, the Examiner also alleges that the instant situation is directly analagous to that which was addressed in *Brenner v. Manson.* (Paper No. 20040227, page 4). Applicants respectfully disagree. In *Brenner*, the issue was not whether a disclosed utility was sufficient. Rather, in the context of an attempt to provoke an interference, the issue in *Brenner* was whether <u>any utility</u> had been disclosed at all (*Id.*

at 534). The only evidence offered by the applicant to demonstrate utility was a reference to an article by a third party showing the activity of a homologue of the subject steroid compound (*Id.* at 521-522). The Examiner's initial basis for refusing to declare an interference was that the applicant had failed to disclose any utility at all (*Id.* at 521). The appellate court agreed that the applicant had done nothing to show or demonstrate that the claimed compound was indeed useful (*Id.* at 521). Thus, it upheld the rejection of the request for declaration of interference (*Id.* at 536). In contrast, the issue in the present case is not whether applicants have disclosed any utility at all, but rather whether or not the instant application teaches at least one utility that meets the requirements of § 101. For the reasons above, applicants respectfully submit that the instant application does teach at least one utility that meets the requirements of §101.

Rejections under 35 U.S.C. §112, first paragraph

Enablement

Claims 38, 52 and 61 were rejected under 35 U.S.C. §112, first paragraph for failing to comply with the deposit requirements. Applicants respectfully submit that the assurance regarding the availability of the deposit, provided below, overcomes this rejection.

Human Genome Sciences, Inc., the assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 (present address). The deposit was made on February 26, 1997, accepted by the ATCC, and given ATCC Accession Number 97904. In accordance with M.P.E.P. § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number 97904 will be irrevocably removed upon the grant of a patent based on

the instant application, except as permitted under 37 C.F.R. § 1.808(b). A partially redacted copy of the ATCC Deposit Receipt for Accession Number 97904 is enclosed herewith as Exhibit A.

Claim 15 was rejected under 35 U.S.C. §112, first paragraph as lacking enablement for an isolated antibody produced by immunizing an animal with any protein whose sequence "comprises" amino acid residues 25-123 of SEQ ID NO:200. Although Applicants respectfully disagree, in the interest of furthering prosecution on the merits, claim 15 has been amended to recite an isolated antibody produced by immunizing an animal with any protein whose sequence "consists of" amino acid residues 25-123 of SEQ ID NO:200. Applicants respectfully submit that the amendment to claim 15 overcomes this rejection.

The Examiner rejects claims 38, 52 and 61 under 35 U.S.C. §112, first paragraph as lacking enablement for "the cDNA contained in ATCC Deposit No. 97904." To the extent that the Examiner's concerns relate to the recitation of only ATCC Deposit No. 97904 in the claims, Applicants submit that the amendments to the claims, by which the claims now recite "the HDGRF73 cDNA contained in ATCC Deposit No. 97904," overcome this rejection. To the extent that this rejection is based on the alleged "lack of a specific marker" or to the extent that the deposit contains multiple different clones, Applicants respectfully traverse.

The Examiner indicates that the lack of a specific marker for SEQ ID NO:200 would result in an antibody raised against multiple different proteins encoded by the multiple different cDNA contained in ATCC Deposit No. 97904. The Examiner also remarks that reproduction of the polypeptides from the deposit would be unpredictable because "it is known that bacteria contain multiple different clones with the same antibiotic resistant [sic] would lead to selective pressure favoring some clones over others and there is no guarantee that the cDNA encoding the polypeptide of SEQ ID NO:200 is going to be selected over time."

Applicants are confused by the Examiner's assertion that Applicants have not provided a "specific marker" for the claimed protein. The amino acid sequence of SEQ ID

NO:200 and/or a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:200, which are provided in the Sequence Listing and correlated to Clone ID HDGRF73 in Table 1 (page 119), can be used by a skilled artisan to as a "specific marker" to select clones containing the claimed HDGRF73 cDNA. For example, one of ordinary skill in the art could have employed either of the methods described in Example 1 of the present specification (page 159) to isolate a cDNA of interest. By transforming the DNA contained within ATCC Deposit No. 97904 into host cells, one of ordinary skill in the art could generate a population of isolated colonies each containing a particular cDNA plasmid. Following transformation, screening with an oligonucleotide complementary to the DNA encoding SEQ ID NO:200 would enable easy identification of the isolated transformant(s) containing the cDNA plasmid of interest. Thus, contrary to the Examiner's assertion, the fact that "bacteria contain multiple different clones with the same antibiotic resistant [sic]" does not render reproduction of the polypeptides from the deposit extremely unpredictable. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Written Description

Claims 1-74 were rejected under 35 U.S.C. §112, first paragraph as lacking written description for any protein that "comprises" amino acid residues 25-123 of SEQ ID NO:200 (as recited in claim 15) and for antibodies or portions thereof that specifically bind a polypeptide "encoded by the cDNA contained in ATCC Deposit No. 97904" (claims 38, 52 and 61).

As a preliminary matter, Applicants respectfully note that this rejection was raised against claims 1-74 in general. However, the rejection only refers specifically to claims 15 (which would include dependent claims 16-23), 38, 52 and 61 (which encompass claims 38-74 when dependencies are included). Applicants respectfully request clarification as to whether or not the Examiner intended this rejection to apply to claims 1-14 and 24-27.

Insofar as the rejection is applied to claims 15-23 and 38-74, Applicants respectfully submit that the amendments to the claims overcome this rejection. Specifically, claim 15 has been amended to recite an isolated antibody produced by immunizing an animal with any protein whose sequence "consists of" amino acid residues 25-123 of SEQ ID NO:200. Claims 38, 52 and 61 have been amended to refer to the "HRGDF73 cDNA contained in ATCC Deposit No. 97904." Applicants therefore request withdrawal of this rejection.

CONCLUSION

The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Applicants believe that there are no fees due in connection with the filing of this paper. However, should a fee be due, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Dated: June 14, 2004

Respectfully submitted,

By_____

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